MAJOR ARTICLE

Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50–59 Years

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(See the Editorial Commentary by Li et al, on pages 929–30.)

Background. Herpes zoster (HZ) adversely affects individuals aged 50–59, but vaccine efficacy has not been assessed in this population. This study was designed to determine the efficacy, safety, and tolerability of zoster vaccine for preventing HZ in persons aged 50–59 years.

Methods. This was a randomized, double-blind, placebo-controlled study of 22 439 subjects aged 50–59 years conducted in North America and Europe. Subjects were given 1 dose of licensed zoster vaccine (ZV) (Zostavax; Merck) and followed for occurrence of HZ for ≥1 year (mean, 1.3 years) postvaccination until accrual of ≥96 confirmed HZ cases (as determined by testing lesions swabs for varicella zoster virus DNA by polymerase chain reaction). Subjects were followed for all adverse events (AEs) from day 1 to day 42 postvaccination and for serious AEs (SAEs) through day 182 postvaccination.

Results. The ZV reduced the incidence of HZ (30 cases in vaccine group, 1.99/1000 person-years vs 99 cases in placebo group, 6.57/1000 person-years). Vaccine efficacy for preventing HZ was 69.8% (95% confidence interval, 54.1–80.6). AEs were reported by 72.8% of subjects in the ZV group and 41.5% in the placebo group, with the difference primarily due to higher rates of injection-site AEs and headache. The proportion of subjects reporting SAEs occurring within 42 days postvaccination (ZV, 0.6%; placebo, 0.5%) and 182 days postvaccination (ZV, 2.1%; placebo, 1.9%) was similar between groups.

Conclusions. In subjects aged 50–59 years, the ZV significantly reduced the incidence of HZ and was well tolerated.

Clinical Trials Registration. NCT00534248.

Herpes zoster (HZ), caused by reactivation of latent varicella zoster virus (VZV) within dorsal root or cranial nerve ganglia, is a unilateral vesicular rash and pain in the involved dermatome [1]. The acute and chronic pain (postherpetic neuralgia [PHN]) associated with HZ interferes with daily functioning and lowers health-related quality of life [2–5]. The incidence, severity, and duration of HZ pain and PHN increase with increasing age [6–10]. Among individuals aged 50–59 years in the United States, the incidence of HZ is 4.2–5.3 per 1000 persons-years, and HZ affects 168 000–212 000 persons per year [7, 8]. A large population-based study in adults aged ≥22 years showed that the proportion of people with HZ who suffered acute pain lasting <30 days was similar in those aged 50–59 years and those aged 60–69 years (87% vs 83%, respectively) and that non-pain complications, such as neurological, ocular, and skin complications, were equally frequent in the 2 age groups [11].

The Shingles Prevention Study (SPS) demonstrated that the live, attenuated zoster vaccine (ZV) (Zostavax; Merck Sharp & Dohme Corp., Whitehouse Station, NJ) reduced the burden of illness due to HZ in persons aged

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≥60 years by 61%; the incidence of PHN by 66%; and the incidence of HZ by 51% [12]. The efficacy of the ZV for preventing HZ decreased with increasing age (64% in subjects aged 60–69 years; 41% in subjects aged 70–79 years; and 18% in subjects ages ≥80 years) [13].

Cell-mediated immunity (CMI) is critical to the containment of VZV [14, 15]. The age-related increase in incidence of HZ is closely linked to an age-related decrease in VZV-specific CMI (VZV-CMI) [16–19]. The ZV induced a significant increase in VZV-specific immunity when measured in a subcohort of the SPS, using 3 different modalities (responder cell frequency, interferon gamma enzyme-linked immunospot, and antibody measured by glycoprotein enzyme-linked immunosorbent assay). All 3 correlated with protection from HZ [14]. Immunogenicity of the ZV declines with increasing age [14, 19] and was noninferior in subjects aged 50–59 years and subjects aged ≥60 years [20]. The ZV was approved in some countries for prevention of HZ in people aged ≥50 years on the basis of immunogenicity without clinical efficacy data in individuals aged 50–59 years

This manuscript describes the study findings based upon the primary objective of determining the efficacy of the ZV for preventing HZ in persons aged 50–59 years and the secondary objective of assessing the overall safety and tolerability of the ZV in these subjects. In a separate publication, the immunogenicity of the ZV (secondary objective) and the association of the antibody response at week 6 postvaccination with the risk of HZ (tertiary objective) in this age group will be reported.

METHODS

Study Design

This was an event-driven, randomized, double-blind, placebo-controlled, multicenter (105 sites) study conducted in North America and Europe between October 2007 and January 2010. Subjects were followed for occurrence of HZ for ≥1 year until 96 confirmed HZ cases had accrued. A total of 22 439 subjects were randomized in a 1:1 ratio according to a site-balanced randomization schedule to receive either the ZV or a placebo. An independent data monitoring committee reviewed safety data and the progress of the study.

Study Population

Healthy subjects aged 50–59 years with a history of varicella or residence in a VZV-endemic area (an area in which chickenpox is a common childhood disease) for ≥30 years were eligible for the study. Persons with immune compromise resulting from disease (eg, human immunodeficiency virus, cancer) or treatments (eg, corticosteroids, chemotherapy, transplant recipients) were excluded. Other exclusion criteria were similar to those used in the SPS [12]. The protocol was conducted in accordance with principles of good clinical practice and approved by the ethical review committee of each participating country/site; written informed consent was obtained from each subject prior to study entry.

An interactive voice response system (IVRS) was used to randomize subjects to vaccination group assignments according to a central computer-generated schedule. The IVRS subsequently assigned to each subject a vial of ZV or placebo, and diluent, each packaged with a unique component identification number that corresponded to the subject's randomized vaccination group.

Intervention

The lyophilized ZV and placebo were supplied in 0.7-mL single-dose vials and stored at −15°C or colder. The placebo contained the same stabilizers as the ZV but no live virus or virus components. ZV and placebo were reconstituted with sterile diluent immediately prior to administration. All subjects received a single 0.65-mL subcutaneous injection of either ZV or placebo in the deltoid area.

Follow-up

Subjects were educated regarding the signs and symptoms of HZ and instructed to call their study site if HZ symptoms or any serious, unexpected, or severe adverse events (SAEs) occurred. Monthly contact by IVRS was made until study completion to ensure that symptoms suggestive of HZ were reported. Subjects reporting HZ symptoms were evaluated by a site investigator to determine if the subject had a suspected HZ case and to initiate treatment, if indicated. Subjects with suspected HZ were entered into 21 days of HZ case follow-up. Subjects were contacted by telephone at 4 and 6 months postvaccination to ensure that all SAEs were reported and at an end-of-study close-out interview.

Efficacy Evaluation

Assessment of Suspected HZ Cases

HZ rash characteristics were recorded and lesion swabs were submitted to Merck for detection of VZV, herpes simplex, and human β-globin DNA using a polymerase chain reaction (PCR) assay [21]. Subjects who developed suspected HZ were treated with antiviral therapy and pain medication according to the judgment of the treating physician in accordance with usual clinical practice.

Every 3 days during the 21-day period following rash onset, subjects were asked to rate their acute HZ-related pain (least, average, worst) in the prior 24 hours on a 0 (no pain) to 10 (worst pain imaginable) rating scale using the Zoster Brief Pain Inventory (ZBPI), a validated measure of HZ-related pain [3, 22].

Determination of Confirmed HZ Cases

Suspected HZ cases were defined as ''confirmed HZ'' if VZV DNA was present by PCR of the skin lesion. If the PCR assay was positive for β-globin or HSV DNA and negative for VZV DNA, then the case was defined as ''not HZ.'' If there was no

specimen or the specimen was inadequate, case confirmation was decided by a clinical evaluation committee consisting of 6 blinded physicians with HZ expertise that evaluated all suspected cases of HZ.

Safety Evaluation

On day 1, subjects were vaccinated and provided a vaccination report card to record all adverse experiences (AEs) from day 1 to day 42 postvaccination (the primary safety follow-up period). During the secondary safety follow-up period (days 43–182 postvaccination), subjects were followed for SAEs. Vaccine-related SAEs and deaths were reported for the entire study.

Statistical Analysis

Efficacy

The primary efficacy endpoint was the incidence of HZ in the ZV and placebo groups, defined as the number of confirmed HZ cases per 1000 person-years of follow-up following vaccination. For a confirmed HZ case, the follow-up time for HZ surveillance was the number of days from vaccination to HZ onset. For a subject who did not develop a confirmed HZ case, the follow-up time for HZ surveillance was the number of days from vaccination to the subject's last day of study follow-up. Vaccine efficacy for HZ (VE_{HZ}) was the relative reduction in incidence rate of HZ in the ZV group compared with that in the placebo group. With a total of ≥96 HZ cases accrued, the study provided an overall power of >90% to detect VE_{HZ} = 64% at 1-sided .025 level. The statistical success criterion corresponds to the lower bound of the overall 2-sided 95% confidence interval (CI) for VE_{HZ} being >25%. Hypothesis test and corresponding CI were based on an exact conditional method [23]. Efficacy analyses were based on an intent-to-treat (ITT) approach, which included all randomized subjects, unless otherwise specified. A modified-intention-to-treat (MITT) analysis was also conducted, which excluded confirmed HZ cases that occurred within 30 days postvaccination.

To summarize HZ acute pain score over time, severity-by-duration scores were utilized. For each confirmed HZ case, the severity-by-duration score of HZ acute pain is the area under the curve (AUC) score defined by the ZBPI HZ pain response curve from HZ onset date through day 21 after HZ onset [12]. The AUC score is zero for all subjects who did not develop a confirmed HZ case. The mean severity-by-duration score among all randomized subjects was a composite measure of HZ incidence, severity, and duration of HZ acute pain. For the ZV or placebo group, the mean score was the sum of the severity-by-duration score for each subject divided by the total number of subjects in that group.

Safety

The proportions of subjects with any AE, injection-site AE, systemic AE, SAE, vaccine-related SAE, and discontinuation due to an AE during the 42-day safety follow-up period were summarized for each vaccination group. Risk differences on these overall safety parameters between the 2 groups and corresponding 2-sided 95% CI on the risk difference were provided using an asymptotic method.

The primary safety endpoint was the incidence of SAEs observed during the 42-day postvaccination follow-up period in each vaccination group. Risk ratio, corresponding 95% CI, and *P* value were calculated using an asymptotic method. The associated 2-sided 95% CI for the single group proportion was calculated using the exact binomial method. Similar analysis was also performed for the 182-day postvaccination follow-up period.

RESULTS

Characteristics of the Study Subjects

As shown in Figure 1, 21 105 (94%) randomized subjects completed the study. Subjects in both groups were comparable with respect to baseline characteristics (Table 1). Approximately 90% of subjects in both groups had 1 or more underlying medical conditions, the most common being hypertension (28.6%). Over 80% of subjects in both vaccination groups were receiving 1 or more medications at baseline and during the study. The most frequently reported concomitant medications were analgesics (∼28%), lipid-reducing agents (∼26%), and renin-angiotensin inhibitors (∼21%).

Efficacy

Subjects in the ITT population were followed for an average of 1.3 years (range, 0 days–2 years) postvaccination for the development of suspected HZ, and 277 suspected HZ cases were evaluated. Among these, 148 (53%) (79 in ZV group, 69 in placebo group) were deemed not HZ, including 112 that had a negative PCR. The remaining 129 (47%) had confirmed HZ (30 in ZV group; 99 in placebo group), including 111 cases that had a positive PCR (86% of confirmed HZ) (24 in ZV group, 87 in placebo group). No subject developed a second confirmed HZ case.

Compared with the placebo, the ZV significantly reduced the incidence of HZ. The estimated VE_{HZ} was 69.8% (95% CI, 54.1%–80.6%) in the ITT analysis (Table 2), which met the prespecified success criterion for this endpoint. In the MITT analysis, the overall estimated VE_{HZ} was 72.4% (95% CI, 57.0%–82.9%).

To evaluate the durability of VE_{HZ}, the time period from randomization to the end of the study was divided into four consecutive periods: 0–0.5 years, >0.5–1.0 years, >1.0–1.5 years, and >1.5 years (Table 2). Based on these data, VE_{HZ} remained fairly stable over the study follow-up period.

The mean severity-by-duration pain score among all the subjects in the ZV group was lower (0.13) than the placebo group (0.49). The estimated relative reduction in this pain score between the 2 groups was 73.0% (95% CI, 52.7, %–84.6%).

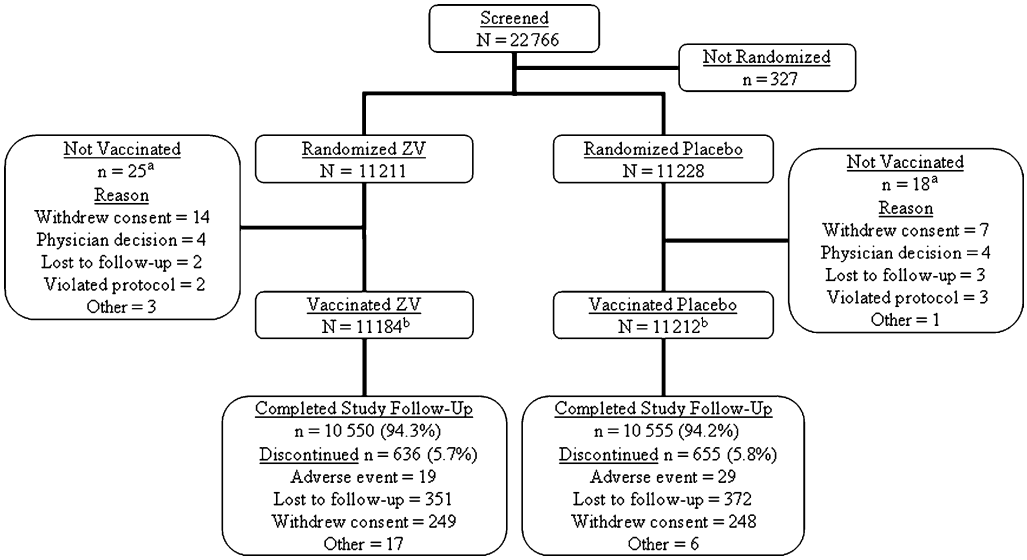

Figure 1. Subject disposition. [a] These 43 subjects were included in the intent-to-treat efficacy analyses but not safety analyses. [b] Six subjects assigned to zoster vaccine (ZV) received placebo/diluent; 4 subjects assigned to placebo received ZV.

Among HZ cases, mean severity-by-duration scores were similar in those who received ZV (49.8) and placebo (56.0). In both groups, the worst pain scores were highest within the first 8 days after HZ onset, and then generally decreased during the remainder of the 21-day follow-up period. Among HZ cases, 57.1% of subjects in the ZV group and 62.2% of subjects in the placebo group had 2 or more reports of worst HZ pain scores ≥3 on the ZBPI.

Safety

Safety follow-up was obtained for more than 99% of subjects in each vaccination group (Table 3). Approximately 73% of subjects reported ≥1 AE in the ZV group compared with 42% in the placebo group, primarily due to different rates of injection-site AEs (ZV, 64%; placebo, 14%; risk difference, 49.5; 95% CI, 48.4–50.6). Very low proportions of injection-site AEs were rated as severe in intensity (ZV, 0.7%; placebo, 0.1%). Systemic clinical AEs were reported by approximately 35% and 34% of ZV and placebo recipients, respectively. Among the reported systemic AEs, 6.7% in the ZV group and 4.7% in the placebo group were deemed to be vaccine-related (risk difference, 2.0; 95% CI, 1.4–2.6).

The most commonly reported systemic AE was headache (ZV, 9.4%; placebo, 8.2%), which was deemed vaccine-related in ∼3% and ∼2% in the ZV and placebo groups, respectively. When headache was excluded from analyses, there was no significant difference in vaccine-related systemic AEs between the two vaccination groups (risk difference, 1.17; 95% CI, −0.0–2.4).

The proportion of subjects reporting SAEs occurring within the 42–days period postvaccination was similar in the ZV (0.6%) and placebo (0.5%) groups (relative risk, 1.13; 95% CI,.81–1.60). The proportion of subjects reporting SAEs occurring within the 182 days postvaccination was also similar in the ZV (2.1%) and placebo (1.9%) groups (relative risk, 1.11; 95% CI, .92–1.33). The only SAE assessed as vaccine-related by a study investigator was an anaphylactic reaction 15 minutes following vaccination in a subject in the ZV group. The subject was treated with epinephrine and methylprednisolone. A recurrence of symptoms required re-treatment; the event resolved later the same day.

Forty-eight subjects had fatal SAEs over the duration of the study (18 in ZV group, 30 in placebo group). For the entire study population, the observed mortality rates (per 1000 person-years)

Table 1. Subject Characteristics

	Zoster Vaccine (N = 11 211)		Placebo (N = 11 228)	
	No.	%	No.	%
Gender				
Male	4298	38.3	4256	37.9
Female	6913	61.7	6972	62.1
Age (y)				
Mean ± SD	54.9 ± 2.8		54.8 ± 2.8	
Race				
White	10, 588	94.4	10 601	94.4
Black or African American	468	4.2	476	4.2
Asian	80	0.7	68	0.6
Other[a]	75	0.7	83	0.7

Abbreviation: SD, standard deviation.

[a] Other includes American Indian or Alaska Native, Multiracial, Native Hawaiian or Other Pacific Islander.

Table 2. Incidence of Confirmed Herpes Zoster Cases

	Zoster Vaccine (N = 11 211)				Placebo (N = 11 228)				
Population	HZ Cases	No.	Total Follow-up[a]	Estimated Incidence[b]	HZ Cases	No.	Total Follow-up[a]	Estimated Incidence[b]	Vaccine Efficacy (95% CI)
ITT (entire study duration)	30	11 211	15 042.85	1.99	99	11 228	15 009.62	6.60	69.8% (54.1–80.6)
ITT 0.0–0.5 years	9	11 186	5536.77	1.62	39	11 210	5541.08	7.04	76.9% (51.5–90.2)
ITT >0.5–1.0 years	13	10 954	5420.64	2.40	36	10 953	5407.72	6.66	64.0% (30.4–82.5)
ITT >1.0–1.5 years	7	10 747	3513.60	2.00	20	10 712	3496.06	5.72	65.2% (14.3–87.6)
ITT >1.5 years	1	3743	571.84	1.75	4	3728	564.76	7.08	75.3% (−149.5–99.5)
MITT	26	11 165	14 124.16	1.84	94	11 189	14 091.27	6.67	72.4% (57.0–82.9)

Abrreviations: CI, confidence interval; HZ, herpes zoster; ITT, intent-to-treat population; MITT, modified intent-to-treat population.

[a] Total follow-up calculated as person-years.

[b] Estimated incidence calculated as per 1000 person-years.

were similar in both vaccination groups (1.18 in ZV group, 1.90 in placebo group; $P = .11$). None of the deaths was determined by the investigator to be vaccine-related.

Of the 34 HZ and HZ-like rashes reported from Days 1 to 42 postvaccination, 24 specimens were available and adequate for PCR testing; wild-type was detected for 3 subjects in the ZV group and 7 subjects in the placebo group. Of the 124 varicella and varicella-like rashes reported from Days 1 to 42 postvaccination, 23 specimens were available and adequate for PCR testing; VZV was detected from 1 varicella-like rash in a subject in the ZV group, but the virus strain could not be determined.

DISCUSSION

This study demonstrated that the ZV reduced the incidence of HZ by nearly 70% in persons aged 50–59 years. Approximately 20% of cases of HZ occur in adults aged 50–59 years [8], so this study result will be of interest to clinicians who take care of patients aged 50–59 years and to patients in that age group who may be interested in reducing their risk of zoster. The estimated VE_{HZ} when the ZV was administered to persons aged 50–59 years was close to that observed in persons aged 60–69 years (63.9%) in the SPS and greater than that observed in persons aged ≥70 years (37.6%). The higher VE_{HZ} in this study than in the SPS likely represents a more robust VZV-specific CMI boost among the younger individuals, as age is a strong determinant of the immune response to ZV and vaccine-induced VZV-specific immune responses correlate with protection from HZ [14, 20, 24, 25] (unpublished data, Merck Sharp and Dohme Corp).

The total burden of acute pain (severity-by-duration) for the study arm receiving ZV was significantly lower than the total

Table 3. Clinical Adverse Experience Summary (days 1–42 postvaccination)

	Zoster Vaccine		Placebo		Difference (95% CI)
	No.	%	No.	%	
Subjects vaccinated and safety follow-up	11 094		11 116		
With one or more AE	8080	72.8	4613	41.5	31.3 (30.1–32.6)
Injection-site AEs	7089	63.9	1596	14.4	49.5 (48.4–50.6)
Systemic AEs	3932	35.4	3722	33.5	2.0 (.7–3.2)
With vaccine-related AEs[a]	7213	65.0	1988	17.9	47.1 (46.0–48.3)
Injection-site AEs[a]	7089	63.9	1596	14.4	49.5 (48.4–50.0)
Systemic AEs[a]	746	6.7	526	4.7	2.0 (1.4–2.6)
With serious AEs	69	0.6[c]	61	0.5[c]	0.1 (−.1–.3)
Serious vaccine-related AEs[a]	1	0.0	0	0.0	0.0 (0–.1)
Who died[b]	1	0.0	3	0.0	0.0 (0–0)

The same subject may appear in different categories but is counted only once in each category.

Abbreviations: AEs, adverse events; CI, confidence interval.

[a] Determined by the investigator to be possibly, probably, or definitely related to the vaccination.

[b] All deaths were determined not vaccine-related by the investigator.

[c] Relative risk of 1.13 (95% CI, .81–1.60).

burden in the placebo group, but solely among HZ cases the burden of acute pain (severity-by-duration) was similar in the 2 treatment arms. This indicates that most of the vaccine effect on acute pain was due to the prevention of HZ and there was no significant attenuation of the severity of cases. This is also consistent with the SPS, which demonstrated that the relative vaccine effect on preventing HZ versus attenuating HZ decreased with advancing age of the vaccinee [12, 26].

The acute pain in the patients aged 50–59 years is similar to that experienced in the acute phase by older people [27], which is important because a large proportion in the younger age group are regularly employed, and HZ results in significant loss of work time as well as diminished productivity in those remaining at work [28]. In a survey-based study, working persons aged 50–59 years with HZ reported 26.5 ± 4.8 absence hours and the equivalent of 71.4 ± 11.7 hours of lost productivity while at work [28].

The ZV was generally well tolerated in this age group. SAEs occurring within the 42 days postvaccination were lower in this study (ZV, 0.6%; placebo, 0.5%) than the SPS (ZV, 1.4%; placebo, 1.4%).

Study limitations are important to note. Issues regarding consistency of diagnosis are a concern in any large, multicenter study. In this study, the HZ incidence in placebo recipients was consistent with expectations for this age group, HZ cases were primarily determined by PCR, and the number of non-cases was the same in both groups, providing reassurance on consistency of HZ case designation. The study only measured acute pain and provided no data on the effect of ZV on PHN in this age group; the sample size needed to determine effect on PHN would be prohibitively large. In older adults in the SPS, VE_{HZ} persisted for a median of 3.1 years (range, 31 days–4.9 years) of follow-up [12]. The current study does not add to the existing data on the duration of the vaccine effect, although VE_{HZ} was stable over the average of 1.3 years of follow-up. The duration of VE_{HZ} in persons aged 50–59 years should be at least as long as that observed in the SPS because the booster response should be more robust in younger people [14].

In conclusion, in persons aged 50–59 years, ZV substantially reduced the incidence of HZ and was generally well tolerated.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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